REMARKS

Claims 51, 53, 54, 56, 59 and 68-77 are pending in this application. Claim 75 has been amended herein for clarity.

Reconsideration of the rejections is respectfully requested in view of the amendment and remarks presented below.

Claims 51, 53, 54, 56, 59, 68, 69, 73, 74 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over "Yamamoto" (Yamamoto et al. Eur. J. Biochem. 143:133-144, 1984) in view of "Benita" (Benita et al. Eur. J. Nucl. Med. 6:515-52, 1981) and further in view of Canfield (WO 87/00289) (Office action paragraph 6).

The rejection is respectfully traversed by the demonstration of "unexpected results" over the cited references.

In this rejection, the Examiner has cited Yamamoto for the teaching that thyroglobulin from thyroid tumor contains less sialic acid (and has other differences) "than does thyroglobulin isolated from normal tumor tissue" (page 3, lines 10-13). (Applicants respectfully submit that the Examiner has misstated this sentence, meaning rather to state that Yamamoto teaches that thyroglobulin from thyroid tumor contains less sialic acid than thyroglobulin isolated from normal **thyroid** tissue.) The Examiner also states that Yamamoto teaches that the use of ConA can differentiate thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal thyroid. The Examiner does not cite the specific portion of Yamamoto relied upon, but would appear to be referring to the

use of a ConA-Sepharose column discussed on page 134, column 1, first paragraph; page 135, column 2, third paragraph, with results in Table 2; page 141, column 2; and page 143, column 1, last paragraph.

As understood by Applicants, the Examiner is stating that Yamamoto provides a suggestion for distinguishing normal from malignant thyroid based on the carbohydrate moiety of the thyroglobulin, and that the known fact that thyroglobulins are secreted into the blood suggests testing blood for thyroglobulins having different carbohydrate moieties, for the purpose of detecting thyroid malignancy. This suggestion is relevant to the present claims as exemplified by claim 51, which recites in step (c):

> c) determining the malignancy of a thyroid tumor by comparing the calculated ratio of the amounts measured in (b)(i) and (b)(ii) with a corresponding predetermined ratio from a reference fluid sample originating from a living body having, a normal thyroid or a benign thyroid;
>
> wherein the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample having the normal or benign thyroid.

Related recitations are found in the other independent claims.

Applicants assert, however, that the present invention as claimed provides unexpected results and benefits over the cited references. In particular, Applicants note that the only apparent suggestion for these steps of the claims is found in the Yamamoto et al. reference, in particular on page 142, second column, second paragraph, in which Yamamoto discusses ratios of different oligosacchararide moieties in the A-I'-b samples, which are from thyroglobulin from malignant thyroid tissue. Also, on page 143, the reference states: "It was found by means of ConA-Sepharose affinity chromatography that thyroglobulin from malignant thyroid gland is richer in triantennary

complex-type oligosaccharides than thyroglobulin **from normal tissues** (data not shown)." (emphasis added).

In traversing the rejection, Applicants note that Yamamoto et al. has only discussed comparison of thyroglobulin from malignant thyroid gland to that from **normal tissues**, that is, normal thyroid as recited in the present claims. However, the present invention is a method for determination of malignancy of a thyroid tumor which can distinguish the malignant thyroid disease from normal and **benign** thyroid tumor. Moreover, the method in the present invention requires a comparison to values for benign thyroid.

Applicants here present a declaration under 37 CFR 1.132, by Kenji NAKAMURA, that demonstrates, in particular, that the distinguishing of normal thyroid from **benign thyroid** is possible using the present invention as claimed, and this aspect of the present invention is not suggested by Yamamoto et al. Therefore, this represents an unexpected benefit of the present invention.

The Declaration presents data obtained using an anti Tg antibody which does not bind to Tg bound to LCA, and which is labeled anti Tg-1. For each sample tested, the total Tg, the amount of Tg bound to LCA, the amount of Tg not bound to LCA and the ratio (%) of Tg bound to LCA/total Tg are determined. Samples from three groups: normal thyroid (1), benign thyroid adenoma (2) and thyroid carcinoma (3), are compared.

As may be seen in Fig. 1 of the Declaration, the amounts of total Tg overlapped between the three groups, and total Tg cannot distinguish between any of the three groups. In fact, the range of total Tg for benign thyroid adenoma is larger than that for thyroid carcinoma, meaning that no values of total Tg definitely indicate thyroid carcinoma. This is similarly true for the amount of Tg bound

to LCA, shown in Fig. 2, and the amount of Tg not bound to LCA, shown in Fig. 3.

Fig. 4 presents the ratio of Tg bound to LCA/total Tg. Here, it can be seen that the values of this parameter **completely** distinguish benign thyroid (2) and thyroid carcinoma (i.e., malignant) (3) from normal thyroid (1).

Moreover, of particular significance is that a subset of the malignant thyroid, those samples having ratio values below about 30%, are **completely distinguished from benign thyroid**, for which values range from about 30 to 50%. This is an example of what is recited in claims 51, 53, 56, 59 68, 69, 73 and 74: "wherein the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample having the **normal or benign thyroid**".

Applicants assert that there is no suggestion in Yamamoto et al. or in any of the cited references for a determination of malignancy based on the determination when the ratio is significant higher or lower than **benign** thyroid, as required by the present claims. Applicants assert that the claimed methods have a benefit not suggested by the prior art, and that claims 51, 53, 54, 56, 59, 68, 69, 73, 74 and 77 are novel and non-obvious over Yamamoto et al., Benita and Canfield, taken separately or in combination.

Claims 51, 53, 54, 56, 59, 68, 69, 73, 74 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over "Tarutani" (Tarutani et al. Biochem. 98:851-857, 1985) in view of Benita and further in view of Canfield (Office action paragraph 7).

This rejection of claims 51, 53, 54, 56, 59, 68, 69, 73, 74 and 77 is respectfully traversed.

The Examiner cites Tarutani for the teaching that thyroglobulin derived from thyroid tumors exhibits different ConA affinity than does thyroid from normal tumors.

Although Tarutani does describe ConA separation of different types of thyroglobulins, Applicants respectfully assert that Tarutani does not provide a clear indication that these types can be quantified.

More significantly, none of the cited references appears to associate the different types of Tg with thyroid malignancy. Without a suggestion or motivation to compare the calculated ratios as recited in the present claims, no *prima facie* case of obviousness can be made for present claims using these references. Applicants therefore assert that claims 51, 53, 54, 56, 59, 68, 69, 73, 74 and 77 are novel and non-obvious over Tarutani, Benita and Canfield, taken separately or in combination.

Claims 70-72, 75 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarutani or Yamamoto in view of Benita and Canfield, and further in view of Robbins (U.S. Patent No. 5,902,725) (Office action paragraph 8).

The rejection of claims 70-72, 75 and 77 is respectfully traversed on the basis of unexpected results and benefits of the present claims.

Applicants have argued above that Tarutani, Benita and Canfield do not appear to suggest any determination of malignancy based on a ratio of a type of thyroglobulin. Applicants have asserted (in response to Office action paragraph 6) that the present claims have unexpected benefits

over Yamamoto, and that Yamamoto does not suggest the specific recitation of the present claims with regard to benign thyroid.

Robbins discloses an assay for cancer of the prostate in which a sample is assayed for prostate specific antigen having a linked oligosaccharide which is at least triantennary. The Examiner refers specifically to the method in column 6, line 57, to column 7, line 18, in which a compound or binding molecule that binds to oligosaccharides that are at least antennary is incubated with the sample, and the sample is then contacted with an antibody supported on a solid support. This antibody recognizes an epitope of the prostate specific antigen, but cannot bind if there is previous binding of the binding molecule (column 7, lines 7-12).

The Examiner differentiates claims 70-72, 75 and 77 from the other pending claims because these claims recite the use of the second anti-thyroglobulin antibody, which does not bind to thyroglobulin to which the lectin or specific antibody is bound. The Examiner has extrapolated Robbins' method for oligosaccharides on PSA to thyroglobulin.

However, Applicants submit that Robbins does not suggest the particular step of determining a sample "to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample having the normal or benign thyroid". Likewise, the present claims provide unexpected results and benefits over the cited references, as presented in the attached Declaration under 37 CFR 1.132, discussed above.

Applicants therefore assert that claims 70-72, 75 and 77 are novel and non-obvious over Tarutani, Yamamoto, Benita, Canfield and Robbins taken separately or in combination.

Claims 51, 53, 54, 56, 59 and 68-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods based on differential lectin binding, does not reasonably provide enablement for methods based on differential binding of antibodies specific for Lewis type sugar chains (Office action paragraph 9).

The rejection of claims 51, 53, 54, 56, 59 and 68-77 under 35 U.S.C. 112, first paragraph, is respectfully traversed.

The method using antibodies as recited in these claims differs from the method using lectins only, in the addition of an antibody rather than a lectin in the method. Since antibodies specific for Lewis type sugar chains are well known in the art, it would be a simple matter for one of skill in the art to obtain and substitute such an antibody for the lectins discussed in the specification. Since such a substitution could be easily performed by one of skill in the art, it is not necessary for enablement purposes to provide in the specification a specific protocol or a working example using the antibody.

Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite (Office action paragraph 10).

The rejection is overcome by the amendment to the claim. Applicants have amended both occurrences of "and/or" in the claim to be –and–.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicants undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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Enclosures: Version with markings to show changes made
Declaration

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

75. (Amended) A method for determining malignancy of a thyroid tumor comprising:

(a) dividing a fluid originating from a living body into a first portion and a second portion;

(b)(i) adding to the first portion a specific lectin or a specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin but not capable of binding to a sugar chain of a second type of thyroglobulin,

to form a conjugate of the first type of thyroglobulin with the specific lectin or the specific antibody; then

(ii) adding to the first portion an antibody-2, capable of binding to the two types of thyroglobulin but not capable of binding to the thyroglobulin to which the specific lectin or the specific antibody is already bound, to form a conjugate of the second type of thyroglobulin with the antibody-2; ~~and/or~~ and

(iii) measuring the amount of the second type of thyroglobulin on the basis of the measurement of the second type of thyroglobulin with antibody-2 conjugate formed in step (b)(ii); ~~and/or~~ and

(c)(i) measuring an amount of the total thyroglobulin of the second portion; and

(ii) determining an amount of the first type of thyroglobulin from the difference between an amount of the total thyroglobulin and the amount of the second type of thyroglobulin obtained in step (b)(iii);

(d) calculating a ratio of (a) the amount of the first type of thyroglobulin to the amount

of total thyroglobulin; or (b) the amount of second type of thyroglobulin to the amount of total thyroglobulin; and

(e) determining the malignancy of a thyroid tumor by comparing the calculated ratio with a corresponding predetermined ratio from a reference fluid sample originating from a living body having a normal thyroid or a benign thyroid;

wherein the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample of the normal or benign thyroid.